

## Exhibit B

Sections 10-21, 16-6, 16-7, 16-8, and 16-56 from  
Smith, M.B., and March, J. March's Advanced Organic Chemistry,  
5<sup>th</sup> ed., Wiley (New York, N.Y., 2001)

## 10-19 Alkylation With Onium Salts

## ALKOXY-DE-HYDROXYLATION

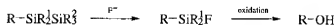
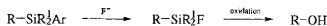


Oxonium ions are excellent alkylating agents, and ethers can be conveniently prepared by treating them with alcohols or phenols.<sup>696</sup> Quaternary ammonium salts can sometimes also be used.<sup>697</sup>

OS VIII, 536.

## 10-20 Hydroxylation of Silanes

## HYDROXY-DE-SILYLALKYLATION

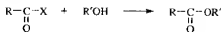


Alkylsilanes can be oxidized, with the silyl unit converted to a hydroxy unit. This requires either an aryl group<sup>698</sup> or another silyl group<sup>699</sup> attached to silicon. Treatment with a fluorinating agent such as tetrabutylammonium fluoride or CsF replaces Ar or SiR<sub>3</sub> with F, which is oxidized with hydrogen peroxide or a peroxy acid to give the alcohol. This sequence is often called the *Tamao-Fleming oxidation*.<sup>698</sup> There are several variations in substrate that allow versatility in the initial incorporation of the silyl unit.<sup>700</sup>

## D. Attack by OR at an Acyl Carbon

## 10-21 Alcoholysis of Acyl Halides

## ALKOXY-DE-HALOGENATION

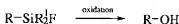
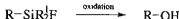


The reaction between acyl halides and alcohols or phenols is the best general method for the preparation of carboxylic esters. It is believed to proceed by a S<sub>N</sub>2 mechanism.<sup>701</sup> As with 10-8, the mechanism can be S<sub>N</sub>1 or tetrahedral.<sup>559</sup> Pyridine catalyzes the reaction by the nucleophilic catalysis route (see 10-9). The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX formed. When aqueous alkali is used, this is called the *Schotten-Baumann procedure*, but pyridine is also frequently used. Both R and R' may be primary, secondary, or tertiary alkyl or aryl. Enolic esters can also be prepared by this method, though C-acylation competes in these cases. In difficult cases, especially with hindered acids or tertiary R', the alkoxide can be used instead of the alcohol.<sup>702</sup> Activated alumina has also been used as a catalyst, for tertiary R'.<sup>703</sup> Thallium salts of phenols give very high yields of phenolic esters.<sup>704</sup> Phase-transfer catalysis has been used for hindered phenols.<sup>705</sup> Zinc has been used to couple alcohols and acyl chlorides.<sup>706</sup> Selective acylation is possible in some cases.<sup>707</sup>

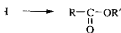
ION



g agents, and ethers can be conveniently prepared from alcohols or phenols.<sup>696</sup> Quaternary ammonium salts



silyl unit converted to a hydroxy unit. The silyl group<sup>699</sup> attached to silicon. Tributylammonium fluoride or CsF replaces a hydrogen peroxide or a peroxy acid to give the *Tamao-Fleming oxidation*.<sup>698</sup> Then the versatility in the initial incorporation of

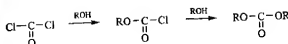


alcohols or phenols is the best general method.

It is believed to proceed by a  $\text{S}_{\text{N}}2$  mechanism. It can be  $\text{S}_{\text{N}}1$  or tetrahedral.<sup>599</sup> Pyridine catalysis route (see 10-9). The reaction is of the  $\text{S}_{\text{N}}2$  type and does not interfere. A base is frequently added. An aqueous alkali is used, this is called the *Williamson ether synthesis*. The alkoxide is also frequently used. Both R and R' can be alkyl or aryl. Enolic esters can also be prepared in these cases. In difficult cases, R', the alkoxide can be used instead of the alkoxide as a catalyst, for tertiary R'.<sup>700</sup> Yields of phenolic esters.<sup>704</sup> Phase-transfer catalysts.<sup>705</sup> Zinc has been used to couple alcohols and phenols.<sup>707</sup> acylation is possible in some cases.

REACTION 10

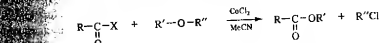
phosgene is the acyl halide, haloformic esters or carbonates can be prepared.



An important example is the preparation of carbobenzoxy chloride ( $\text{PhCH}_2\text{OCOCI}$ ) from phosgene and benzyl alcohol. This compound is widely used for protection of amino groups during peptide synthesis (see 10-55).

Acyl halides react with thiols, in the presence of zinc, to give the corresponding thioesters.<sup>708</sup>

Acyl halides can also be converted to carboxylic acids by using ethers instead of alcohols, in MeCN in the presence of certain catalysts such as cobalt(II) chloride.<sup>709</sup>

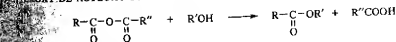


This is a method for the cleavage of ethers (see also 10-71).

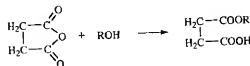
OS I, 12; II, 142, 144, 167, 187, 623, 714; IV, 84, 263, 478, 479, 608, 616, 788; VI, 166, 168, 171; VII, 199, 259, 312, 824; VIII, 190; VIII, 257, 516.

## 10-22 Alcoholysis of Anhydrides

### ALCOXY-DE-ACYLOXY-SUBSTITUTION



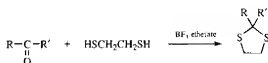
The scope of this reaction is similar to that of 10-21. Though anhydrides are somewhat less reactive than acyl halides, they are often used to prepare carboxylic esters. Acids, Lewis acids, and bases are often used as catalysts—most often, pyridine.<sup>710</sup> Catalysis by pyridine is of the nucleophilic type (see 10-9). 4-(*N,N*-dimethylamino)pyridine is a better catalyst than pyridine and can be used in cases where pyridine fails.<sup>711</sup> Nonbasic catalysts are cobalt(II) chloride<sup>712</sup> and  $\text{EtCl}_2\text{-SiO}_2$ .<sup>713</sup> Formic anhydride is not a stable compound but esters of formic acid can be prepared by treating alcohols<sup>714</sup> or phenols<sup>715</sup> with acetic-formic anhydride. Cyclic anhydrides give monoesterified dicarboxylic acids, for example,



Alcohols can also be acylated by mixed organic-inorganic anhydrides, such as triphosphoric anhydride,  $\text{MeCOOP}(\text{OH})_2$  (see 10-35).<sup>716</sup>

OS I, 285, 418; II, 69, 124; III, 11, 127, 141, 169, 237, 281, 428, 432; IV, 15, 242, 304; V, 8, 459, 591, 887; VI, 121, 245, 560, 692; 486; 441, 258.

acetals, are stable in the presence of bases, except that a strong base can remove the aldehyde proton, if there is one (see 10-107).<sup>86</sup> A common method for the protection of ketones involves treatment with ethanedithiol to give a cyclic dithioketal.<sup>87</sup> In subsequent reactions involving the R or R' group, the protecting group can be

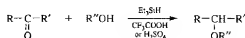


be removed by 10-6. Alternatively, the dithioketal can be desulfurized with Raney nickel (14-34), giving the overall conversion  $C=O \rightarrow CH_2$ . Dithioacetals can also be prepared from aldehydes or ketones by treatment with thiols in the presence of  $TiCl_4$ ,<sup>88</sup>  $SiCl_4$ ,<sup>89</sup> with a disulfide (RSSR; R = alkyl or aryl),<sup>90</sup> or with methyltrimethylsilane (MeSSiMe<sub>3</sub>).<sup>91</sup>

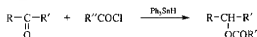
OS I, 1, 298, 364, 381; II, 137; III, 123, 387, 502, 536, 644, 731, 800; IV, 21, 479, 679; V, 5, 292, 303, 450, 539; VI, 567, 666, 954; VII, 59, 149, 168, 177, 241, 276, 297; VIII, 357. Also see OS IV. 558-588; V. 25; VIII. 415.

### 16-6 Reductive Alkylation of Alcohols

### C-HYDRO-O-ALKYL-ADDITION



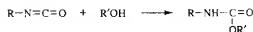
Aldehydes and ketones can be converted to ethers by treatment with an alcohol and triethylsilane in the presence of a strong acid<sup>92</sup> or by hydrogenation in alcoholic acid in the presence of platinum oxide.<sup>93</sup> The process can formally be regarded as addition of ROH to give a hemiacetal  $R'R''C(OH)OR'$ , followed by reduction of the OH. In this respect, it is similar to 16-14. In a similar reaction, ketones can be converted to carboxylic esters (reductive acylation of ketones) by treatment with an acyl chloride and triphenyltin hydride.<sup>94</sup>



Ethers have also been prepared by the reductive dimerization of two molecules of an aldehyde or ketone (e.g., cyclohexanone  $\rightarrow$  dicyclohexyl ether). This was accomplished by treatment of the substrate with a trialkylsilane and a catalyst.<sup>95</sup>

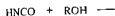
### 16-7 The Addition of Alcohols to Isocyanates

### N-HYDRO-C-ALKOXY-ADDITION



16

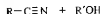
amates (substituted urethanes). This is an excellent reaction. Amino acid HNCO gives unsymmetrical ureas.  $\text{H}_2\text{N}-\text{R}-\text{NH}_2$  gives *allophanates*.



reactions are made by compounds containing two OI (RNHCSOR'),<sup>96</sup> though the details of the mechanism is certainly attacking elucidates the kinetic picture analyzed by metallic compounds<sup>101</sup> or *n*-butyllithium (OS I, 140; V, 162; VI, 95,

### Alcoholysis of Nitrile

## OXY-OXO-DE-NITRIL-TER



the addition of dry HCl to a solution of the ester leads to the hydrochloride (salts and imino ethers). The ester can be converted to the free base by treatment with sodium bicarbonate, or it can be converted to the corresponding carboxylic ester by treatment with sodium hydroxide, in which case aqueous workup is required. Imino esters can be converted to the free base by treatment with sodium hydroxide, in which case aqueous workup is required.

This reaction is of broad scope for acyclic R and for nitro compounds. The reaction is not applicable for the synthesis of mononitriles and with no diester formed. Cyanogen chloride reacts with  $\text{HCl}$  or  $\text{AlCl}_3$  to give car-



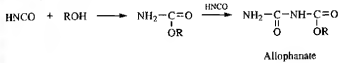
The alcohol ROH can also be used in the synthesis of the ester ROAc. See, for example, QS I, 5, 270; II, 284, 310.

that a strong base can remove the common method for the protection to give a cyclic dithioacetal.<sup>97</sup> After up, the protecting group can be



it can be desulfurized with Raney  $\text{Ni}$  to  $\text{CH}_2$ . Dithioacetals can also be removed with thiols in the presence of  $\text{KOH}$  or  $\text{NaOH}$  or with methylthiol. 32, 536, 644, 731, 800; IV, 21, 47, VII, 59, 149, 168, 177, 241, 271; VIII, 415.

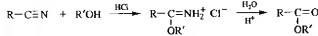
carbamates (substituted urethanes) are prepared when isocyanates are treated with alcohols. This is an excellent reaction, of wide scope, and gives good yields. Hydrogen cyanide  $\text{HCN}$  gives unsubstituted carbamates. Addition of a second mole of  $\text{HCN}$  gives *allophanates*.



Urethanes are made by combining compounds with two  $\text{NCO}$  groups with compounds containing two  $\text{OH}$  groups. Isothiocyanates similarly give thiocarbamates ( $\text{RNHCSOR}'$ ),<sup>96</sup> though they react slower than the corresponding isocyanates. The details of the mechanism are poorly understood,<sup>97</sup> though the oxygen of the alcohol is certainly attacking the carbon of the isocyanate. Hydrogen bonding complicates the kinetic picture.<sup>98</sup> The addition of  $\text{ROH}$  to isocyanates can also be catalyzed by metallic compounds,<sup>99</sup> by light,<sup>100</sup> or, for tertiary  $\text{ROH}$ , by lithium amides<sup>101</sup> or *n*-butyllithium.<sup>102</sup> 32, 536, 644, 731, 800; IV, 21, 47, VII, 59, 149, 168, 177, 241, 271; VIII, 415.

### 16-3. Alcoholysis of Nitriles

#### 16-3-1. OXY,OXO-DE-NITRIL-O-TERSUBSTITUTION



by treatment with an alcohol and by hydrogenation in alcoholic acid solutions can formally be regarded as  $\text{OR}''$ , followed by reduction of the  $\text{OR}''$  to  $\text{OR}$ . In a similar reaction, ketones can be converted to alcohols by treatment with an

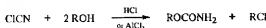


the dimerization of two molecules of dicyclohexyl ether). This was catalyzed by trialkylsilane and a catalyst.<sup>95</sup>

les



The addition of dry  $\text{HCl}$  to a mixture of a nitrile and an alcohol in the absence of water leads to the hydrochloride salt of an imino ester (imino esters are also called imidates and imino ethers). This reaction is called the *Pinner synthesis*.<sup>103</sup> The salt can be converted to the free imino ester by treatment with a weak base such as sodium bicarbonate, or it can be hydrolyzed with water and an acid catalyst to the corresponding carboxylic ester. If the latter is desired, water may be present from the beginning, in which case aqueous  $\text{HCl}$  can be used and the need for gaseous  $\text{HCl}$  is eliminated. Imino esters can also be prepared from nitriles with basic catalysts.<sup>104</sup> This reaction is of broad scope and is good for aliphatic, aromatic, and heterocyclic  $\text{R}$  and for nitriles with oxygen-containing functional groups. The application of the reaction to nitriles containing a carboxyl group constitutes a good method for the synthesis of mono esters of dicarboxylic acids with the desired group protected and with no diester or diacid present. Cyanogen chloride reacts with alcohols in the presence of an acid catalyst such as  $\text{HCl}$  or  $\text{AlCl}_3$  to give carbamates.<sup>105</sup>



The alcohol  $\text{ROH}$  can also be added to nitriles in another manner (16-56). 32, 536, 644, 731, 800; IV, 21, 47, VII, 59, 149, 168, 177, 241, 271; VIII, 415.

by using the benzoylated cyanohydrin as one of the components in a phase-transfer catalyzed process. By this means products can be obtained from aldehydes which normally fail to self-condense.<sup>860</sup>

OS I, 94; VII, 95.

### 16-55 Addition of Radicals to C=O, C=S, C=N Compounds

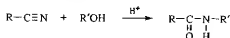
Radical cyclization is not limited to a radical attacking a C=C unit (see 15-35 and 15-36), and reactions with both C=N and C=O moieties are known. Reaction of  $\text{MeON}=\text{CH}(\text{CH}_2)_3\text{CHO}$  with  $\text{Bu}_3\text{SnH}$  and AIBN, for example led to *trans*-(methoxyamino)cyclopentanol in good yield.<sup>861</sup> Addition of radical to the C=N unit of  $\text{R}-\text{C}=\text{N}-\text{SPh}$ <sup>862</sup> or  $\text{R}-\text{C}=\text{N}-\text{OBz}$ <sup>863</sup> led to cyclic imines. Radical addition to simple imines leads to aminocycloalkenes.<sup>864</sup> Radical also add to the carbonyl unit of phenylthio esters to give cyclic ketones.<sup>865</sup>

## Reactions in Which Carbon Adds to the Hetero Atom

### A. Oxygen Adding to the Carbon

#### 16-56 The Ritter Reaction

N-HYDRO, N-ALKYL-C-OXO-BIADDITION

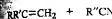


Alcohols can be added to nitriles in an entirely different manner from that of Reaction 16-8. In this reaction, the alcohol is converted by a strong acid to a carbocation, which adds to the negative nitrogen, water adding to the carbon:



The immediate product tautomerizes to the N-alkyl amide. Only alcohols that give rise to fairly stable carbocations react (secondary, tertiary, benzylic, etc.); primary alcohols do not give the reaction. The carbocation need not be generated from an alcohol but may come from protonation of an alkene or from other sources. In any case, the reaction is called the *Ritter reaction*.<sup>866</sup> Hydrogen cyanide also gives the reaction, the product being a formamide. Trimethylsilyl cyanide has also been used.<sup>867</sup> Since the amides (especially the formamides) are easily hydrolyzable to amines, the Ritter reaction provides a method for achieving the conversions  $\text{R}'\text{OH} \rightarrow \text{R}'\text{NH}_2$  (see 10-46) and alkene  $\rightarrow \text{R}'\text{NH}_2$  (see 15-8) in those cases where  $\text{R}'$  can form a relatively stable carbocation. The reaction is especially useful for the preparation of tertiary alkyl amines because there are few alternate ways of preparing these compounds. The reaction can be extended to primary alcohols by

ment with triflic an  
ence of the nitrile.  
Alkenes of the form R  
mercuric nitrate to give  
obtained by the Ritter  
g acids.



The Ritter reaction  
( $\text{NHCONHR}'$ ).<sup>871</sup>  
OS V, 73, 471.

### 16-57 Acylation of Al

ACYL-C-ACYLOXY-AD

R-

Aldehydes can be con  
presence of  $\text{BF}_3$ , other  
not normally be appl  
the reagent is trichloroa  
catalyst.<sup>875</sup>  
OS IV, 489.

### 16-58 The Addition of

When catalyzed by aci  
cyclic acetals, the mos  
formaldehyde is calle  
*paraldehyde*. Under ce  
Aldehydes can also pol  
is required to form hen  
formed from formaldeh  
aldehydes are aceta  
Because formaldehyd  
convenient to use them

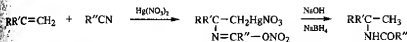
omponents in a phase-transfer  
obtained from aldehydes 1

### =N Compounds

g a C=C unit (see 15-35 and  
eties are known. Reaction of  
for example led to *trans*-  
ion of radical to the C=N unit  
lic imines. Radical addition to  
also add to the carbonyl unit

ment with triflic anhydride<sup>868</sup> or  $\text{Ph}_2\text{CCl}^+ \text{SbCl}_6^-$  or a similar salt<sup>869</sup> in the  
presence of the nitrile.

Alkenes of the form  $\text{RCH}=\text{CHR}'$  and  $\text{RR}'\text{C}=\text{CH}_2$  add to nitriles in the presence  
mercuric nitrate to give, after treatment with  $\text{NaBH}_4$ , the same amides that would  
obtained by the Ritter reaction.<sup>870</sup> This method has the advantage of avoiding  
strong acids.

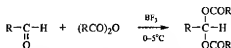


The Ritter reaction can be applied to cyanamides  $\text{RNHCN}$  to give ureas  
( $\text{RNHCNHR}'$ ).<sup>871</sup>

OS V, 73, 471.

### 16-57 Acylation of Aldehydes and Ketones

#### ACYL-C-ACYLOXY-ADDITION



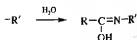
Aldehydes can be converted to *acylals* by treatment with an anhydride in the  
presence of  $\text{BF}_3$ , other Lewis acids,<sup>872</sup> proton acids,<sup>873</sup> or  $\text{PCl}_3$ .<sup>874</sup> The reaction  
cannot normally be applied to ketones, though an exception has been reported when  
the reagent is trichloroacetic anhydride, which gives acylals with ketones without a  
catalyst.<sup>875</sup>

OS IV, 489.

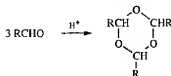
### 16-58 The Addition of Aldehydes to Aldehydes



fferent manner from that of  
erted by a strong acid to a  
er adding to the carbon:



nide. Only alcohols that give  
iary, benzylic, etc.); primary  
ed not be generated from  
r from other sources. In any  
rogen cyanide also gives the  
silyl cyanide has also been  
s) are easily hydrolyzable to  
achieving the conversions  
e 15-8) in those cases where  
n is especially useful for the  
are few alternate ways to  
nded to primary alcohols by



When catalyzed by acids, low molecular weight aldehydes add to each other to give  
cyclic acetals, the most common product being the trimer.<sup>876</sup> The cyclic trimer of  
formaldehyde is called *trioxane*,<sup>877</sup> and that of acetaldehyde is known as  
*paraformaldehyde*. Under certain conditions, it is possible to get tetramers<sup>878</sup> or dimers.  
Aldehydes can also polymerize to linear polymers, but here a small amount of water  
is required to form hemiacetal groups at the ends of the chains. The linear polymer  
formed from formaldehyde is called *paraformaldehyde*. Since trimers and polymers  
of aldehydes are acetals, they are stable to bases but can be hydrolyzed by acids.  
Because formaldehyde and acetaldehyde have low boiling points, it is often  
convenient to use them in the form of their trimers or polymers.